

**CLAIMS**

1. A biochip assembly (2) for a cell based assay (1) of the type comprising a biochip (20) having an elongate microchannel (21), an inlet port (22) mounted adjacent a proximal end (23) of the microchannel (21) and an outlet port (24) mounted adjacent a distal end (25) of the microchannel (21) and a liquid delivery unit (3) for the transmission of liquid through the biochip (20) the liquid delivery unit (3) having at least one liquid delivery port (37) characterised in that there is provided:-
- 5
- 10 a plurality of separate biochips (20);
- at least one separate reservoir well (30) for each biochip (20) which is not permanently fluidically coupled thereto; and
- 15 a plurality of removable separate enclosed transfer conduits (40) for releasable connection of some of the ports (35, 22, 24) and some of the ports (35, 22, 24) and wells (30).
- 20 2. A biochip assembly (2) as claimed in claim 1, in which the liquid delivery unit (3) has a separate delivery port (35) for each biochip (20).
3. A biochip assembly (2) as claimed in claim 1 or 2, in which two or more wells (30) are provided for each biochip (20).
- 25 4. A biochip assembly (2) as claimed in any preceding claim, in which there are two sets of at least two wells (30), one set adjacent the inlet port (22) and the other set adjacent the outlet port (24).
- 30 5. A biochip assembly (2) as claimed in any preceding claim, in which the transfer conduit (40) has an internal cross-sectional area substantially greater than that of the microchannel (21) of each biochip (20).
6. A biochip assembly (2) as claimed in any preceding claim, in which each

biochip (20) has more than one inlet port (22), each of which is for connection to a different liquid delivery unit (3).

- 5 7. A biochip assembly (2) as claimed in any preceding claim, in which each biochip (20) has more than one outlet port (24).
8. A biochip assembly (2) as claimed in any preceding claim, in which the biochip (20) comprises a pair of elongate microchannels (21(b), 21(c)), each having at least one inlet port (22(b), 22(c)) at its proximal end (23(b), 23(c)) and at their distal ends (25(c), 25(b)) connecting into a further microchannel (21(d)) having at least one outlet port (24(d)) at its distal end (25(d)) to form therewith a Y-shaped composite microchannel.
- 10 9. A biochip assembly (2) as claimed in any of claims 1 to 7, in which the biochip (20) comprises an elongate microchannel (21) having a bore, at least one intermediate portion (21(a)) of which has a different cross-sectional area to that of the rest of the microchannel (21).
- 15 10. A biochip assembly (2) as claimed in any of claims 1 to 7, in which each biochip (20) comprises a pair of elongate microchannels (21(g), 21(h)), each microchannel (21(g), 21(h)) having at least one inlet port (22(g), 22(h)) and at least one outlet port (24(g), 24(h)), the microchannels (21(g), 21(h)) being connected their proximal ends (23(g), 23(h)) and distal ends (25(g), 25(h)).
- 20 11. A biochip assembly (2) as claimed in any preceding claim, in which the microchannels (21) are all formed on one bottom face (13) of a planar biochip sheet (15) of translucent plastics material as open cut-out channels covered by a thin film of polymer material (16) coated with a pressure sensitive adhesive material, the other top face (12) of the biochip sheet (15) mounting the input ports (22), the output ports (24) and the reservoir wells (30).
- 25 30 12. A biochip assembly as claimed in claim 11, in which the microchannels are of non-cylindrical cross-section.

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13. A biochip assembly (2) as claimed in claim 11 or 12, in which there is provided a further open cut-out channel forming a main liquid feeder channel (36), the main liquid feeder channel (36) having a liquid delivery port (37) for connection to the liquid delivery unit (3) and a plurality of delivery ports (35) equal in number to the number of biochips (20), the liquid feeder channel (36) being covered by a thin film of plastics material.
14. A biochip assembly (2) as claimed in any of claims 11 to 13, comprising:-
- an upper support plate (46) having an upper face (47) and a lower face (48) in use; and
- a plurality of tubes (45) mounted in the plate (46) and projecting proud of the faces (47, 48), each tube (45) proud of the upper face (47) being for connection to one of the transfer conduits (40) and at its other end for connection to one of the ports (22, 24) and wells (30).
15. A biochip assembly (2) as claimed in claim 14, in which releasable connection means (63) is provided for mounting the plate (46) above the top face (12) of the biochip sheet (15) in correspondence with ports (35), (22), (24) or wells (30).
16. A biochip assembly (2) as claimed in claim 14 or 15 in which the releasable connection means (63) comprises:-
- a pair of spaced-apart columns (65) proud of the biochip sheet (15) and mounting a pivot bar (66) therebetween; and
- a support member (67) pivotally mounted on the bar (66) and having a channel-shaped elongate open mouthed slot (68) for reception of the plate (46), portion of the support member (67) forming a camming surface (69) for engaging the top face (12) of the biochip

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sheet (15) when pivoted into a position to engage the plate (46) above the biochip sheet (15).

17. A biochip assembly (2) as claimed in any of claims 11 to 16, in which when  
5 the biochips (20) each have additional inlet ports (22) and there are additional sets of main liquid feeder channels (36), the number of such sets equals the number of additional inlet ports (22) for each biochip (20).
18. A biochip assembly (2) as claimed in any of claims 11 to 17, in which the  
10 inlet ports (22) and outlet ports (24) on the top face (12) have bores between entrance and exit, of substantially constant cross-sectional area and of substantially the same order of magnitude as that of the microchannels (21).
19. A biochip assembly (2) as claimed in any preceding claim, in which the liquid  
15 delivery unit (3) comprises:-
- a liquid outlet link assembly (50) to provide a steady liquid delivery  
20 output rate below 10 $\mu$ l per minute through the liquid delivery port (37) of the liquid delivery unit from a link input port (56) connected to a positive displacement pump (51) forming part of the liquid delivery unit (3) and having an immediate step pumping rate substantially greater than the desired steady liquid delivery output rate, the liquid outlet link  
25 assembly (50) further comprising a hollow link body (61) having a resistance to flow therethrough substantially less than through the liquid delivery port (37); and
- pressure stabilising means (70) for the link body (61) formed by  
30 pressure compressible means connected thereto whereby, on increased pressure being encountered in the hollow link body (61) on operation of the positive displacement pump (51), the pressure compressible means (71) initially contracts to counteract the pressure rise in the liquid outlet link assembly (50) and hence the rise in the liquid flow rate through the liquid delivery port (37) and then as delivery

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of liquid takes place through the liquid delivery port (37) expands to maintain the pressure within the liquid link assembly relatively stable.

- 5      20.      A biochip assembly (2) as claimed in claim 19, in which the pressure compressible means comprises a gas bubble (71).
- 10      21.      A biochip assembly (2) as claimed in claim 19 or 20, in which the compressible means comprises more than one gas bubble (71) and the aggregate volume of the bubbles (71) is a multiple of the volume of liquid dispensed in one step of the pump (51).
- 15      22.      A biochip assembly (2) as claimed in claim 20 or 21, in which the aggregate volume of the gas bubble or bubbles (71) is significantly larger than the volume of the liquid dispensed in one step of the pump (51).
- 20      23.      A biochip assembly (2) as claimed in any of claims 20 to 22, in which the aggregate volume of the gas bubble or bubbles (71) is comparable to the volume of the pump (51).
- 25      24.      A biochip assembly (2) as claimed in any of claims 20 to 23, in which the aggregate volume of the gas bubble or bubbles (71) is in the range of 10 to 100 microlitres.
- 30      25.      A biochip assembly (2) as claimed in claim 19, in which the compressible means comprises an elastic membrane forming part of the link body (61).
26.      A biochip assembly (2) as claimed in claim 19, in which the link body (61) comprises expandable tubing which forms the expansion means.
27.      A biochip assembly (2) as claimed in any of claims 19 to 26, in which control means is provided and is connected to a flow conditions sensing means (73) for the liquid outlet link assembly (50) for causing the pump (51) to operate to provide the desired flow rate through the outlet port (37).

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28. A biochip assembly (2) as claimed in claim 27, in which the flow conditions sensing means (73) is a pressure sensor connected to the link body (61).
29. A biochip assembly (2) as claimed in claim 27, in which the flow conditions sensing means (73) is an optical flow sensing assembly.
30. A biochip assembly (2) as claimed in claim 29, in which the optical flow sensing assembly comprises a camera (9).
31. A biochip assembly (2) as claimed in any of claims 19 to 30, in which the pump (51) is a syringe pump.
32. A biochip assembly (2) as claimed in claim 31, in which the volume pumped for each step of the syringe pump is of the order of 0.2  $\mu$ l.
33. A cell based assay assembly (1) comprising a biochip assembly (2) as claimed in any preceding claim and detection and recording equipment (4) for conducting an assay on a biological cell as it is delivered through the biochip assembly (2).
34. A cell based assay assembly (1) as claimed in claim 33, in which the detection and recording equipment (4) comprises an optically inverted microscope (7), a digital camera (9) and computerised recording, monitoring and control means (10).
35. A cell based assay assembly (1) as claimed in claim 33 or 34, in which the detection and recording equipment (4) comprises an epifluorescence device (8).
36. A method of conducting a biological cell assay on a cell based assay assembly (1) as claimed in any of claims 33 to 35 comprising the steps of:-
- (a) connecting the liquid delivery outlet port (35) to a well (30) by a transfer conduit (40);

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- (b) aspirating liquid from the well (30) into the transfer conduit (40);
- (c) connecting the transfer conduit (40) to an inlet port (22);
- (d) delivering liquid from the transfer conduit (40) through the biochip (20) and then repeating steps (a) to (d) as often as required; and
- 10 (e) then carrying out the assay with the detection and recording equipment (4) as the final step (d) is being carried out.
37. A method as claimed in claim 36, in which the additional step, after one or more of step (d), is carried out of simultaneously using another transfer conduit (40) to connect the outlet port (22) of the biochip (20) to another well
- 15 (30).
38. A method as claimed in claim 36 or 37, in which when the biochip (20) is manufactured in accordance with any of claims 11 to 18, the additional step is performed, after the assay has been completed, of removing the film (16) and
- 20 carrying out further tests on the biological cells adhering to the film (16).
40. A method as claimed in any of claims 36 to 39, in which the additional step is performed of filling the transfer conduit (40) with the system liquid.
- 25 39. A method as claimed in any of claims 36 to 38, in which the additional step is performed of replacing the transfer conduit (40) between aspirating liquids from wells (30) during steps (a)-(d) in order to avoid cross-contamination.
- 30 41. A method as claimed in any of claims 36 to 39 in which, after aspirating liquid from a well (30), the additional step of flushing system liquid through the transfer conduit (40) is carried out.
42. A method as claimed in any of claims 36 to 41, in which a desired flow rate

( $Q_1$ ) within the biochip assembly (2) is achieved by:-

5 determining the required pressure ( $P_1$ ) within the liquid delivery unit (3) to achieve the desired flow rate ( $Q_1$ ) by first determining a steady flow rate ( $Q_{\text{plunger}}$ ) for the pump (51) which maintains a constant pressure ( $P$ ) within the biochip assembly to provide a fluidic resistance factor ( $R_f$ ) for each biochip (20) determined by dividing the pressure ( $P$ ) by the flow rate  $Q_{\text{plunger}}$  and then multiplying the desired flow rate ( $Q_1$ ) by this fluidic resistance factor ( $R_f$ ) to provide the required pressure ( $P_1$ );  
10 and

then operating the pump (51) to provide the required pressure ( $P_1$ ).

- 15 43. A method as claimed in claim 42, in which when the pressure drops below the required pressure ( $P_1$ ) by a predetermined amount, the pump (51) is operated to deliver liquid into the liquid delivery unit and when the required pressure is exceeded by a predetermined amount, the pump (51) is reversed to aspirate liquid.
- 20 44. A method as claimed in claim 42, in which the flow rate of the pump (51) is varied to maintain the pressure within a predetermined range of pressure.
- 25 45. A method as claimed in any of claims 42 to 44 in which the required pressure ( $P_1$ ) is achieved with a predetermined displacement volume ( $\Delta V$ ) of the pump (51) over a predetermined time by varying the compressibility of the pressure compressible means.
- 30 46. A method as claimed in claim 45, in which the varying of the compressibility of the pressure compressible means comprises adding or reducing the amount of gas within the link body (61).